REMARKS

Status of the Claims

Claims 1-2, 4-5, 8-12, 32, 49, 51-53, and 58-61 are pending and are rejected herein. Claims 1-2, 49, and 51-52 are amended. Claims 3, 6-7, 13-31, 33-48, 50, and 54-57 were canceled previously and claim 32 is canceled herein. No new matter is added in any claim amendment.

Claim amendments

Claims 1 and 49 are amended to recite administering one or more diuretic and to delete "bismuth subnitrate or bismuth subcitrate" and "chelator(s)". Originally filed claim 1 recited "administering a pharmacologically effective dose of at least one adjuvant..." which adjuvant was limited to competitive metal blockers, chelators and diuretics in dependent claims. Therefore, the current amendment to independent claims 1 and 49 does not broaden the scope of the originally filed claims and contains no new matter. As the competitive metal blockers bismuth subnitrate and bismuth subcitrate are deleted from independnet claims 1 and 49, new claims 62-63 are added to depend from amended independent claims 1 and 49, respectively, and a recite a further method step of administering bismuth subnitrate or bismuth subcitrate. New claims 62-63 correspond substantially to deleted original claims 6 and 54 and do not comprise new matter.

Also, in claim 1, the method step of "preventing accumulation" is amended to a "wherein" characterizing clause as preventing accumulation of francium-221 and bismuth-213 is a result of administering the diuretic(s) and the actinium-225 radioimmunoconjugate. In addition, in claim 49 the phrase "inhibiting renal uptake of francium-221 and bismuth-213 comprising" is deleted.

Also, amendments to claims 2 and 51 limit the recitation to "diuretic(s)". In addition, claims 4 and 52 are amended to recite further method steps "further comprising administering one or more chelator that is...".

The 35 U.S.C. §103(a) Rejections

Claims 1-2, 4-5, 8, 10-11, 32, 49, 51-53, and 59-60 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Kennel** *et al.* (Cancer Biotherapy & Radiopharmaceuticals, 15:235-244, 2000) in view of **Satoh** *et al* (Eur. J. Cancer Clin Oncol., 25:1727-2731, 1989), **Jones** *et al.* (Nuclear Medicine & Biolgoy, 1996, 23:105-113) and **Schilcher** *et al.* (J. Can. Res. Clin. Oncol., 1984, 107:57-60), all of record, in further view of **Nair** et al. (J. Radiat. Res. 42:21-37, 2001). Applicants respectfully traverse this rejection.

In considering independent claims 1 and 49, the Examiner states that **Kennel** *et al.* teach a method of treating lung cancer with alpha particles by administering Ac-225 bound to a HEHA-MAb 210B (Abstract). The Examiner also states that **Kennel** *et al.* teach that while the isotope coupled to the targeting monoclonal antibody delivers a tumoricidal dose to the lung, effectiveness of the therapy is limited by the associated radiotoxicity (pg. 242, 2nd col., last PP), for example, animals at necropsy had total ablation of bone marrow cells, splenic atrophy, some damage to the stomach lining and intestines and excess accumulation of undigested food (pg. 240, 1st col. 1st PP).

The Examiner states that **Satoh** *et al.* teach the effects of preinduction of metallotheionein by bismuth subnitrate on the adverse effects and antitumor activity gamma ray irradiation in mice (Abstract) such as reducing bone marrow damage without compromising the tumor reducing effects (pg. 1730, 1st col., last PP). Thus, the Examiner states that **Satoh** et al. teach that bismuth subnitrate pretreatment is an effective method for protection against side effects in radiotherapy (Abstract).

. The Examiner also states that **Jones** *et al.* evaluate dithiol chelating agents DMPS and DMSA as adjuvants administered prior to and after the radioconjugate to accelerate clearance of bismuth and to reduce early and late accumulation of bismuth in the kidney (pg. 109, 2nd col., 1st PP; pg. 112, 1st col. 1st PP & 2nd col., conclusion). In addition the Examiner states that **Schilcher** *et al.* teach using the diruetic furosemide to prevent cumulative nephrotoxicity during an evaluation of fractionated low and high dose cisplatin for various tumors (Abstract). Furthermore, the Examiner states that **Nair** et al. disclose radioprotectors in radiotherapy. The Examiner also states that **Nair** et al. disclose that while acute toxicity has been a main reason for radioprotector failure in

clinical applications, the use of nontoxice amounts of several radioprotectors having a different mechanism of action can overcome the problems associated with their toxicity (pg. 31, last PP).

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to modify the method taught by **Kennel** et al. to include administration of the competitive metal blocker bismuth subnitrate, the chelator DMPS and the diruetic furosemide in view of **Satoh** et al., **Jones** et al. and **Schilcher** et al. because the references disclose that the agents are effective at reducing toxicities associated with readiotherapies. Also, the Examiner concludes that as **Nair** et al. teach combining several radioprotectors having a differenct mechanism of action to overcome problems with radioprotector toxicity, the decision in In re Kerkhoven (205 USPQ 1069 (CCPA 1980) holding that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to obtain a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Thus, the Examiner states that one of ordinary skill in the art would have a reasonable expectation of success in making the modifications. Applicant respectfully disagrees.

Kennel *et al.* disclose an evaluation of Ac-225 for vascular targeted radioimmunotherapy and teach that the potential for Ac-225 as radioimmunotherapeutic agent is compromised most importantly by the radiotoxicity associated with the decay daughter radioisotopes released from the target organ (Abstract). **Kennel** *et al* further teach lack of a conventional chelate that could withstand the energy released by radioactive decay of Ac-225 (page 243, 1st col., lines 2-4).

Satoh *et al.* disclose that the preinduction of metallothionein by bismuth subnitrate may prevent the adverse effects of gamma ray irradiation in mice (Abstract). A dose of 200 mg/kg prior to irradiation with a lethal dose of 6 Hy/leg of cobalt-60 suppressed leukocyte reduction and lipid peroxidation in bone marrow cells and increased metallothionein 2-fold therein (pg. 1728, 2nd col.). It is assumed that bismuth subnitrate induces an increased level of metallothionein which scavenges the free radicals induced by the gamma irradiation and thereby protects the bone marrow from gamma radiation injury (pg. 1729, 2nd col. to page 1730, 1st col., ll. 2).

Jones *et al.* discloses that DMPS, which is more effective than DMSA, can be used as a potential adjuvant chelation therapy in lead-212 or bismuth-212 radioimmunotherapy protocols (Abstract). **Schilcher** *et al* examine the effect of fractionated low and single high dose cisplatin in various tumors. **Schilcher** *et al* state that cisplatin therapy was associated with nephrotoxicity (page 59, col. 2, last PP) and that cumulative nephrotoxicity was prevented by prehydration and/or treatment with furosemide or mannitol (Summary, last sentence), although **Schilcher** *et al* do not support this assertion with any actual data. In fact, nephrotoxicity associated with the cisplatin therapy was observed in three patients (pg. 59, col. 1, 2nd full PP).

Nair et al. review radioprotecting agents categorized as radioprotectors, adaptogens and absorbents (pg. 22, 2nd full PP; Table 1) and hypothesize that using non-toxic amounts of several agents might overcome the toxicities associated with larger doses required when used individually (pg. 31, last PP).

Applicants have canceled claim 32. Applicants' invention, as recited in amended independent claims 1 and 49, is drawn to methods of reducing nephrotoxicity in an individual during radioimmunotherapeutic treatment of a pathophysiological condition and of increasing the therapeutic index of a DOTA-chelated actinium-225 radioimmunoconjugate by administering one or more diuretics to prevent renal accumulation or uptake of francium-221 and bismuth-213 daughters. This action both reduces nephrotoxicity due to the daughters and increases the therapeutic index of actinium-225 upon reduction thereof.

A determination of obviousness requires a teaching or suggestion of all the claim elements in the combination of cited prior art which provides motivation for one of ordinary skill in the art to make the combination with a reasonable expectation of success not found in Applicants' specification. Also, the teachings of the prior art must be considered as a whole. First, as a primary reference, **Kennel** *et al.* specifically state that although HEHA-chelated actinium-225 coupled to a targeting antibody may deliver a tumoricidal dose to the lung, the radiologic side effects due to release of daughter alphas limits the effectiveness of therapy. **Kennel** *et al.* also state that they know of no conventional chelant that would withstand the energy release (pg. 242, 2nd col., last PP). Second, **Kennel** et al. is silent about any way to reduce the radiologic side effects

attibutable to the release of alpha particles from the Ac225 and the daughters. Specifically, the reference neither teaches nor suggests using a diuretic comcomittantly with the Ac225 antibody construct to reduce nephrotoxicity caused be Fr221 and Bi213 release of alpha particles.

Combining **Satoh** et al., **Jones** et al., **Schilcher** et al. or **Nair** et al. with **Kennel** et al. cannot remedy these deficiencies. None of the references teach an Ac225-Mab conjugate nor administering the same as a radioimmunotherapeutic against a pathophysiological condition. **Satoh** et al. and **Jones** et al. only disclose the competitive metal blocker bismuth subnitrate and the chelator DPMS, respectively, which no longer read on amended claims 1 and 49.

Also, contrary to the Examiner's statement, Schilcher et al. do not teach or suggest using a diuretic to prevent nephrotoxicity from a radiometal. **Schilcher** *et al.* only state that cumulative nephrotoxicity from cisplatin chemotherapy was prevented by treatment with the diuretic furosemide, but do not provide any protocols for its use. The platinum in cisplatin is not a radiometal. The nephrotoxicity from cisplatin is due to the platinum whereas the nephrotoxicity from Ac225 administration is due to the alpha particle emission of Fr221 and its daughter Bi213 in the kidneys. This is a significant difference. The mechanisms of action in causing nephrotoxicity of cisplatin and the emitted alpha particles from Fr221 and Bi213 are very different, particularly as the francium and bismuth *per se*, unlike platinum in cisplatin, are not causing the toxicity. A person having ordinary skill in this art would not extrapolate from a nonradiometal to a radiometal with any reasonable expectation of success not found in Applicants' specification particularly as no guidance is given in **Schilcher** et al. how to use the diuretic.

In addition, **Nair** et al. neither teach or suggest that diuretics are radioprotector compounds. In addition, even though Applicants' amended claims 1 and 49 no longer recite a combination, Applicants wish to state that In re Kerkhoven requires the individual elements comprising the combination must be known in the prior art to be useful for the same purpose. Applicants strongly reiterate that the prior art does not teach that diuretics are useful to prevent nephrotoxicity from radiometals. Such teaching comprises a novel and nonobvious disclosure in Applicants invention.

Absent a teaching or suggestion of these claim elements, the combination of **Kennel** et al. with **Satoh** et al., **Jones** et al., **Schilcher** et al. and **Nair** et al. cannot render amended independent claims 1 and 49 obvious. Furthermore, claims 2, 4-5, 8, 10-11, 51-53, and 59-60, and new claims 62-63 depend directly or indirectly from amended claims 1 and 49 and, therefore, also cannot be rendered obvious over the combination. Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 1-2, 4-6, 8, 10-11, 51-53, 58-61 be withdrawn.

Claims 1-2, 4-5, 8-12, 32, 49, 51-53, and 58-61 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Scheinberg** *et al.* (U.S. Pub. No. 2002/0058007) or **McDevitt** *et al.* (Science 2001, 204:1537-1540) in view of **Satoh** *et al*, **Jones** *et al.* and **Schilcher** *et al.*, all of record, in further view of **Nair** et al. Applicants respectfully traverse this rejection.

As a primary reference, in considering independent claims 1 and 49, the Examiner states that **Scheinberg** et al. teach treating cancerous cells with alpha particles by administering a conjugate comprising a functionalized Ac225-DOTA chelate covalently attached to a monoclonal antibody, such as Ac225-DOTA-HuM195 (pg. 2, PP 0016-0017, 0021). The Examiner also states that **Scheinberg** et al. teach that internalization of Ac225 into cancer cells permits emission of alphas from itself or its daughters, but that gastrointestinal mucosal sloughing and bone marrow hyplasia, consistent with severe radiotoxicity, was found in treated mice (pg. 8, PP 0097).

Also, as a primary reference, cited against independent claims 1 and 49, the Examiner states that **McDevitt** et al. teach the functionalized, chelated Ac225-monoclonal antibody conjugates (Abstract; pg. 1538, 1st col. 2nd full PP), the cancers and the method of treating the same (Abstract) as in **Scheinberg** et al. The Examiner also states that **McDevitt** et al. disclose specific tumor uptake of Ac225, but that Bi213 daughter accumulates in the kidney as a result of decay from non-targeted constructs (pg. 1538, Fig. 1B). The Examiner concludes that obviousness is determined by the combination of **Scheinberg** et al. or **McDevitt** et al. with **Satoh** et al., **Jones** et al.,

Schilcher et al. and **Nair** et al. for the same reasons as with **Kennel** et al. described supra.

Satoh et al., **Jones** et al., **Schilcher** et al. and **Nair** et al. are as described separately by the Examiner and by the Applicants supra. **Scheinberg** *et al.* teach actinium-225 complexes comprising actinium-225 chelated to modified chelants and linked to a targeting agent which are delivered to cancerous cells such that the emitted alpha particles from actinium-225 and its daughters effects treatment (Abstract). The actinium-225 complexes may treat solid and disseminated cancers such as prostate cancer, lymphoma, leukemia, neuroblastomas, breast cancer and ovarian cancer (PP 0037). Doses of actinium-225 above the mean tolerated dose cause gastrointestinal mucosal sloughing and bone marrow hyplasia consistent with severe radiotoxicity (PP 0097). Francium-221 and bisumuth-213 daughters from non-targeted actinium-225 complexes accumulate in the kidneys (0108).

McDevitt *et al* examined tumor therapy with targeted atomic nanogenerators (Abstract). **McDevitt** *et al* examined the stability of Ac-225-DOTA-antibody constructs as potent tumor-selective molecular-sized generator in both established solid carcinomas or disseminated cancers (pg. 1538, 1st col, 2nd full PP). **McDevitt** *et al* also teach that the daughters of Ac-225 might be transferred to other sites such as the kidneys and intestine (pg. 1538, col.2, line 14-col.3, line 6).

Applicants have canceled claim 32. Applicants invention, as recited in amended independent claims 1 and 49 is as described supra. Neither **Scheinberg** et al. nor **McDevitt** et al. teach or suggest administering one or more diuretics with the Ac225 conjugate as a way to reduce nephrotoxicity. As discussed supra for **Kennel** et al. and in view of the amendments to claims 1 and 49, neither **Satoh** et al. nor **Jones** et al. teach or suggest diuretics as a means of preventing nephrotoxicity due to alpha emissions from francium-221 and bismuth-213 accumulating in the kidneys. Nor can combining **Schilcher** et al. and **Nair** et al. with **Scheinberg** et al. or **McDevitt** et al. remedy this same deficiency for the reasons discussed supra.

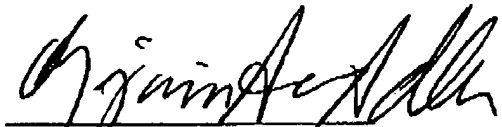
Absent a teaching or suggestion of this claim element, the combination of **Scheinberg** et al. or **McDevitt** et al. with **Satoh** et al., **Jones** et al., **Schilcher** et al. and **Nair** et al. cannot render amended independent claims 1 and 49 obvious. Furthermore,

claims 2, 4-6, 8-12, 51-53, 58-61, and new claims 62-63 depend directly or indirectly from amended claims 1 and 49 and, therefore, also cannot be rendered obvious over the combination. Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 1-2, 4-6, 8-12, 51-53, 58-61 be withdrawn.

This is intended to be a complete response to the Final Office Action mailed April 4, 2008. Applicants submit that claims 1-2, 4-6, 8-12, 49, 51-53, and 58-63 are in condition for allowance and request that claims 1-2, 4-6, 8-12, 49, 51-53, and 58-63 be passed to issuance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution. Applicants believe fees are due for a 1 month extension of time; however, should this be an error, please debit any applicable fees from Deposit Account No. 07-1185, upon which the undersigned is allowed to draw.

Respectfully submitted,

Date: July 22, 2008



Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
Tel.: (713) 270-5391
Fax: (713) 270-5361
BEN@adlerandassociates.com